Formulation and In Vitro Evaluation of Nimodipine as an Orodispersible Film

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Abstract

The objective of this study is to prepare nimodipine as orodispersible films by using solvent casting method in order to enhance its oral bioavailability and improve patient compliance. Nimodipine is a calcium channel blocker belongs to class II, it used to improve neurologic outcome following subarachnoid hemorrhage (SAH) by reducing the incidence and severity of ischemic deficits. ODFs were prepared using three types film forming polymers with different concentration HPMC E3, HPMC E5 and HPMC E15, using (Glycerin) as plasticizer and (Poloxamer 407) as surfactant. The effect of different concentrations and types of polymers, on mechanical properties such as (folding endurance and percent of elongation) and the in-vitro evaluation parameters such (disintegration time, surface pH, weight variation and dissolution profile) were evaluated. HPMC E5 films showed slightly higher cumulative % drug release than films of HPMC E3 and HPMC E15 at the same concentration of plasticizer and surfactant.

Keywords: *Orodisperible films (ODFs), Nimodipine, HPMC E5.*

Introduction

Solubility is an important factor in the drug development process. About 35–40% of the new chemical entities developed are less aqueous soluble results in low bioavailability that is why it is major concern for the scientist to develop and design formulation. The drugs with high permeability and low solubility fall in the category of BCS class II and class IV. Poorly absorbed drugs have slow drug absorption and lead to inadequate bioavailability and gastrointestinal mucosal toxicity [(1)].

Orodispersible films are polymeric matrices that meet numerous necessities for being utilized efficiently as a drug release platform [(2)]. These orodispersible films can be utilized for targeting sensitive site that may not be conceivable with tablets or liquid formulations, hence proving to be a promising candidate for delivery of the drug. Several other names of these thin films have been appeared, for example orodispersible films (ODFs), oral soluble films, oral strips, oral films, buccal films, wafers, ophthalmic films, and transmucosal films. A film that readily dissolves in the oral cavity is generally named as orodispersible film [(3)].

Orodispersible films are fast-dissolving films. It does not require water for the administration and gives quick absorption and instant bioavailability [(4)]. These orodispersible films have predominance over major drawbacks of rapid disintegrating tablets related to fear of choking, friability and can be utilized for dysphasic and schizophrenic patients. These orodispersible films are specialized in a way that the water is not required for administration because they quickly fragments within a few seconds, discharging the drug in mouth[(5)].

The various polymers used in ODFs are sodium CMC, HEC, polyacrylic acid, HPC, hypromellose (semisynthetic), etc., and the natural polymers are Chitosan, alginate, starch, maltodextrin, etc [(6)]. The various plasticizers used in ODFs are: Glycerol, propylene, glycol, polyethylene glycol, sorbitol, etc [(7)].

Nimodipine is a calcium channel blocker. It

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belongs to class II (low solubility – high permeability) according to (BSC) [8]. Nimodipine used as an adjunct to improve neurologic outcome following subarachnoid hemorrhage (SAH) from ruptured intracranial berry aneurysms by reducing the incidence and severity of ischemic deficits by crossing blood brain barrier due to its high lipophilicity and cause relaxation for cerebral artery due to calcium channel blocking [9].

The aim of this work is to prepare nimodipine as orodispersible films in order to enhance its oral bioavailability and improve patient compliance.

Materials and Methods

Nimodipine powder was supplied by Hyper Chem-China, hydroxypropyl methyl cellulose (E3, E5, E15) were supplied from Evonik Germany, polaxamer 407 and crosspovidone obtained from JP & SB Converting Services International S.L. Spain.

Nine formulas were prepared (F1-F9) as listed in (Table 1) by using solvent casting technique; every film of about 4 cm^2 area have 10 mg of nimodipine.

Each quantity of (HPMC) was dissolved in 20 ml of solvent (distilled water) constant stirring is needed for 2 h by using magnetic stirrer in order to form homogenous polymeric solution. Plasticizer was added to this solution and also stirring is required for additional 1 h.

Next step involve dissolving nimodipine, surfactant, saliva stimulating agent and sweetener in 20 ml of water and ethanol as co-solvent (equal quantity from each solvent) in another beaker to form clear solution, mixing the two medium using magnetic stirrer for 1 h, the solution was kept in sonicator for degassing.

Petridish was used to which the bubble free solution was casted on it and kept in hot air oven (50 ^oC) overnight. Dried film was then removed and cut into the desired shape and size (2 cm × 2 cm) for the intended application [10].

Table (1): Composition of Nimodipine Orodispersible Films Formulas

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nimodpine (mg)	10	10	10	10	10	10	10	10	10
HPMC (E3) (mg)	15	25	35						
HPMC (E5) (mg)				15	25	35			
HPMC(E15)(mg)							15	25	35
Polaxamer 407	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Glycerin (ml)	5	5	5	5	5	5	5	5	5
Crosspovidone (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ascorbic acid	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Saccharin	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation of Nimodipine ODFs

Physical appearance of films such as homogeneity, consistency, color and clearness of films were estimated. These were tested by visual examination of films and evaluation of quality by feel or touch [11]. Weight variation test confirms the uniformity of the film formed. Ten randomly selected films from each batch (each of 2 cm × 2 cm) were cutted and weighed individually [12].

Thickness of ODFs was determined by using digital vernier caliper at five different sites (center and four corners). This is necessary to confirm the uniformity in the thickness of the film as it is directly correlated to the exactness of dose in each strip [13].

Folding endurance (FE) measures the elastic properties or the flexibility of films. The FE of ODFs was measured by repetitively collapsing a small stripe of ODFs at the same point until broken or folded up to 300 times. The number of times of folding at which the film remains intact indicates the value of FE [14].

Normally the value of percent of elongation (%E) of films is increases as the amount of plasticizer increases. %E is determined by calculating the differences between the initial and final length of stripe divided by the initial length [15].

Three films (2 cm × 2 cm) were cut randomly from each formulation batch; these films were placed in 50 ml of phosphate buffer pH 6.8 (0.5 % Tween 20) solutions individually and kept on magnetic stirrer for 1 h. Then the solution was filtered, diluted suitably and the amount of drug was calculated by measuring the absorbance of the drug at λ max 238 nm using standard calibration curve of drug in phosphate buffer pH 6.8 [16].

To measure the pH value of ODFs, one stripe was allowed to dissolve in 2 ml of distilled water and the pH of the obtained solution is determined using pH-meter. We expect different pH value due to using different film forming polymers in formulation of ODFs along with the drug [17]. In vitro disintegration time (DT) is measured by using petri dish method. DT is the time at which the ODFs start to breakdown or disintegrate (in second). The test is done by taking 3 films of each patch in petri dish and after adding 2 ml of distilled water for each film, the petri dish was shaken continuously, then measure the time at which the ODFs start to breakdown or disintegrate [18].

In vitro dissolution of nimodipine ODFs was determined through using USP type II dissolution apparatus (i.e. paddle). Nimodipine ODFs allow to dissolve in 500 ml of 6.8 phosphate buffer, the stirrer was modified to rotate at 50 rpm and the temperature of the medium was adjusted at 37 ± 0.5 ºC during the procedure. Then samples (5 ml) were taken by using a syringe at regular intervals (1, 2, 3, 4, 5, 10, 15 and 20 min); before analyzing the withdrawn samples using UV-spectrophotometry at λmax 238 nm they must be filtered by using filter paper (0.45µm). The withdrawn bulk at each time must be replace with fresh 6.8 phosphate buffer in order to maintain sink conditions. Then the dissolution profile of the drug is constructed by plotting the percent of accumulative drug release against the time [19].

Fourier transform infrared spectroscopy (FTIR)

The compatibility between drug and all excipients explained by (FTIR) spectroscopy. The study of compatibility by FTIR performed by making spectrums for nimodipine (pure powdered drug) and spectrum for selected formula.

Results and Discussion

Films that prepared from HPMC (E3, E5 and E15) were opaque white, thin and soft. The average weights for all the prepared formulations were uniform and fit to the referred values (Table 2). The average thickness values of nimodipine ODFs are shown in (Table 2). The results were found to vary between 0.12 to 0.18 mm. The formulated nimodipine ODFs showed an acceptable quantity of medicament ranged from 87.2 % - 109.6 % (Table 2). Nimodipine ODFs showed an acceptable surface pH value (5.7-6.3) (Table 2) when compared to that pH of oral mucosa indicating that it does not cause an irritation to oral mucosa.

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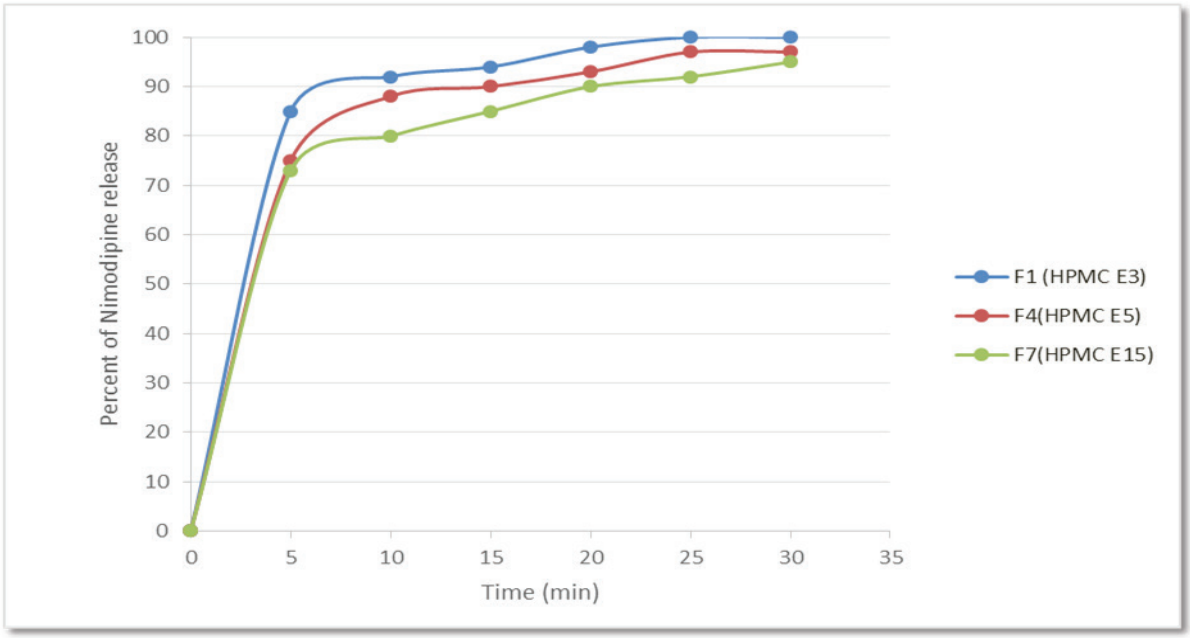
Table (2): Physical Evaluation Parameters of Nimodipine ODFs

Formula	Weight Variation	Thickness	Drug Content	Surface pH	In-Vitro DT
F1	39 ± 3	0.12 ± 0.02	93.4 ± 3.87	6.2 ± 0.2	33± 1.4
F2	46 ± 3	0.15 ± 0.02	95 ± 2.45	6.4 ± 0.1	35 ± 3.2
F3	61 ± 2.1	0.18 ± 0.02	95 ± 3.23	6.1 ± 0.1	38 ± 2.3
F4	41 ± 2	0.13 ± 0.01	97 ± 2.14	6.2 ± 0.22	40 ± 1.2
F5	53 ± 3	0.15 ± 0.02	95 ± 2.23	6.1 ± 0.14	45 ± 1.8
F6	57 ± 3.22	0.15 ± 0.019	96 ± 3.13	6 ± 0.12	50 ± 1.4
F7	48.3 ± 2	0.12 ± 0.02	99 ± 2.1	5.9 ± 0.1	55 ± 2.4
F8	51 ± 2.1	0.13 ± 0.01	98 ± 2.22	5.8 ± 0.12	59 ± 3.3
F9	58 ± 3	0.15 ± 0.01	97 ± 3.1	5.8 ± 0.2	60 ± 3.6

Effect of Different Types of Polymers

Formulas (F3, F6, F9) were utilized to study the influence of type of polymer on the mechanical, physical properties and on the dissolution profile of the nimodipine ODFs while the concentration of polymer remain constant. The mechanical properties of different film forming polymers are shown in (Table 3). The formula (F1) which contains HPMC E3 gave satisfactory % elongation (35 %) but it give low folding endurance values (84). While (F4) (HPMC E5) gave satisfactory % E (31.3) and good FE values (123), also HPMC E3 (F1) was difficult to handle.

shown in (Figure 1), 85% of the drug was released from F1 (HPMC E3) at the first 4 min compared to F4 (HPMC E5) which was released 85% at 7 min. The difference in dissolution may be due to the variances in viscosity grade of HPMC film forming polymer.



Figure(1):Effect of viscosity grade of HPMC polymer on the dissolution profile of nimodipine in phosphate buffer (pH 6.8) at 37°C

Effect of Concentrations of Selected Polymer (HPMC E5)

Formulas (F4, F5 and F6) were utilized to study the influence of different concentrations of HPMC E5 (15, 25 and 35 % w/w) respectively on the mechanical, physical properties and on the dissolution profile of the ODFs. The disintegration time of nimodipine ODFs (F4, F5 and F6) shows DT of the ODFs declined as the HPMC E5 concentration decreased from 35 % in formula (F6) to 25 % in formula (F5) (Table 4). This may be attributed to formation of thick layer of gel which make the diffusion of water inside the film difficult. Similar outcomes were established with lamotrigine fast dissolving films [20], losartan potassium fast dissolving films [21].

The results of mechanical properties exposed in (Table 4) revealed that the % E and folding endurance (FE) increased as the concentration of polymer increase.

This due to the fact that greater polymer concentration leads to heavily crowded chains of HPMC E5 that will need more force to distraction furthermore the increase in the concentration of polymer results in enhance the flexibility of ODFs resulting in high % E values. Similar outcomes were establish with cinnarizine fast dissolving films [22].

Table (3):Mechanical Properties of Nimodipine ODFs from different polymer types

Formula	Folding endurance	Percent of elongation
F1(HPMC E3)	84 ± 2	35 ± 5
F4(HPMC E5)	123 ± 4	31 ± 3
F7(HPMC E15)	136 ± 3	20 ± 2

Table (4): Mechanical Properties of Nimodipine ODFs Formulas (F4, F5 and F6)

Formulas	% E	FE	DT
F4	31± 3	123 ± 4	45
F5	35 ± 1.4	134 ± 3	38
F6	40 ± 0.9	148 ± 2	30

The dissolution profiles of nimodipine from formulas (F4, F5 and F6) are shown in (Figure 2). It was observed that the dissolution rate of nimodipine reduced significantly as the concentration of HPMC E5 was increased from 25 % (w/w) in formula (F5) to 35 % (w/w) in formula (F6). This may be due to the higher concentration of polymer, resulting in production of high consistency gel layer created by close interaction between the particles of HPMC E5 resulting in a diminished movement of medication particles in swollen lattices, which prompts a decline in dissolution rate [23].

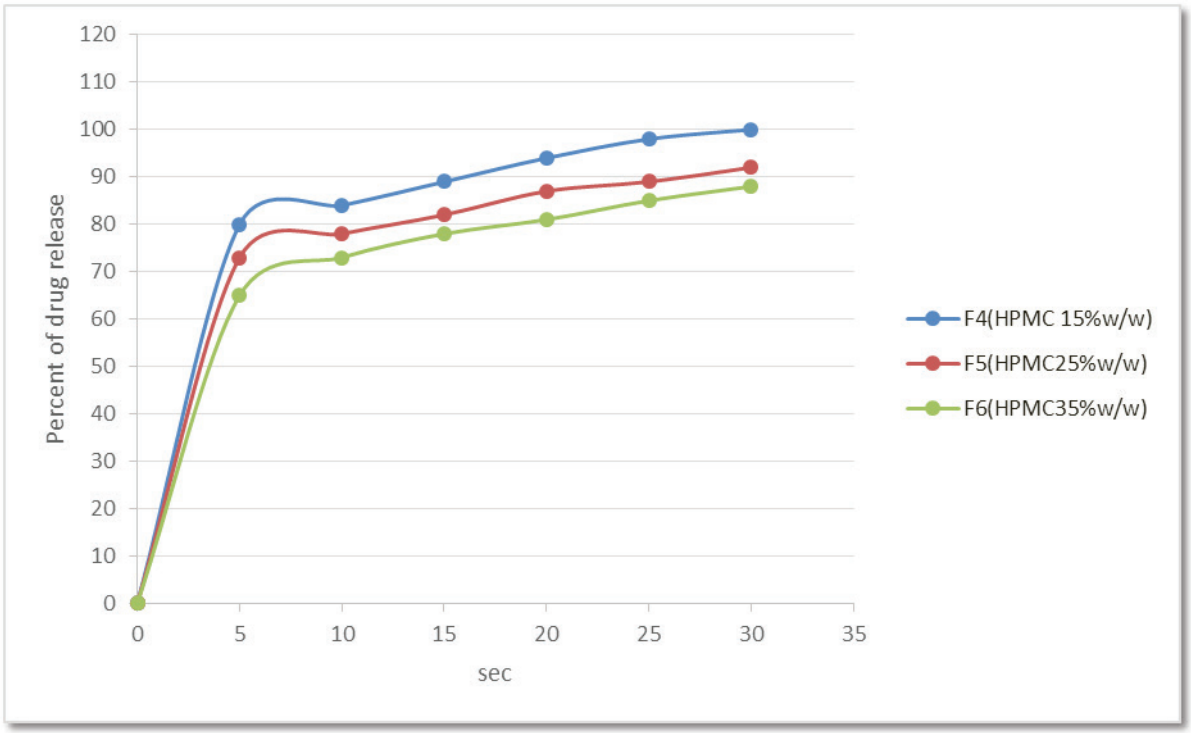


Figure (2): Various concentration of HPMC E5 effect on the dissolution profile of nimodipine in phosphate buffer (pH 6.8) at 37°C .

Conclusions

The best film forming agent among HPMC (E3, E5 and E15) was HPMC E5 because it gives fastest in-vitro disintegration time with an acceptable mechanical properties and dissolution behavior.

Ethical Clearance : Taken from University of Babylon ethical committee

Source of Funding : Self

Conflict of Interest : Nil

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